b.) Remarks

Regarding an initial formal matter, Applicants note the Office Action states it is nonfinal (Office Action Summary) and that it is final (page 5). To clarify the record, Applicants' representative, accordingly, both confirmed with the Examiner and verified on PTO PAIR such has not been made final.

Claims 1, 2-5, 8, 10 and 11 have been amended in order to correct their punctuation, for better idiomatic usage or to delete pharmaceutical salts only. Accordingly, no new matter has been added.

Claims 1-5 and 8-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Suzuki (U.S. Patent No. 5,587,378) in view of Trenkwalder (*Clinical Neuroscience* (1998)), both of record, in further view of Evidente (*Movement Disorders* Vol. 15, No. 2 (2000) 324-27), newly cited.

As discussed, Suzuki teaches administering the xanthine derivative of claim 12 for treating Parkinson's disease. Trenkwalder is cited for

> teach[ing] that another motor phenomenon that occurs in Parkinson's disease is nocturnal myoclonus (page 108, column 3).

That is, Suzuki teaches administering the claimed compounds to Parkinson's patients. In support of the rejection, the Examiner contends it would also be obvious to administer the claimed compounds to treat patients with RLS and nocturnal myoclonus since (i)

> these motor disturbances are commonly observed in individuals with Parkinson's disease[1],

and because (ii) Evidente teaches

> RLS responds well to antiparkinsonian drugs such as levodopa and dopamine agonists.

This rejection is respectfully traversed. To clarify the record, however, Applicants wish to explain the etiology, pathology and clinical features of each of Parkinson's Disease, Restless Legs Syndrome and Nocturnal Myoclonus. For both the Examiner's convenience, and as well as to complete the record, such explanation is provided both below and additionally by way of the enclosed Declaration under Rule 132 of Dr. Tomoyuki Kanda (the "Kanda Declaration").

As is very well-understood by those of ordinary skill in this art, restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressed urge to move the legs and sometimes also other parts of the body, usually accompanied by a highly marked sense of discomfort or pain in the legs or other affected body part. RLS is especially triggered by rest or inactivity, and its symptoms are temporarily relieved or suppressed by movement. Onset of RLS follows a circadian pattern, with symptoms most intense in the evening and nighttime hours, especially when the afflicted individual is lying down. Kanda Declaration at ¶7.

There are two types of RLS: idiopathic RLS, also known as "primary" RLS, which typically has a familial component, and "secondary" RLS, which typically occurs in conjunction with other medical conditions, particularly: iron deficiency anemia,

[1] Respectfully submitted, this argument at least is without logic or factual basis.

pregnancy, and end-stage renal disease. The prevalence of RLS in large-scale population studies are from approximately 6% to 15% for the entire adult range[2]. The symptoms of RLS are frequently relieved by treatment with dopaminergic agents or opioids. Select anticonvulsants and sedative-hypnotics are also effective in some RLS patients. Kanda Declaration at ¶8.

Considerations of peripheral vs central nervous system pathology are based on pharmacologic studies. Dopaminergic agents that cross the blood-brain barrier alter RLS, with L-dopa and dopamine agonists serving to reduce (and dopamine antagonists exacerbating) RLS symptoms[3]. However, dopamine antagonists with limited central action,[4] do not alter RLS symptoms. Thus, combination of a peripheral dopamine antagonist together with a central dopamine agonist has been used to successfully reduce adverse effects without altering the efficacy of the treatment[5]. Kanda Declaration at ¶9.

According to the Examiner, the foregoing suggests a link between RLS and Parkinson's disease.

However, it is understood there is in fact no such link or causality. Specifically, (i) Parkinson's disease does not at all increase the risk for RLS and (ii) RLS

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2 Lavigne et al., "Restless legs syndrome and sleep bruxism: prevalence and association among Canadians", *Sleep*, Vol. 17, No. 8 (1994) 739-43.

3 de Mello, et al., "Treatment of periodic leg movements with a dopaminergic agonist in subjects with total spinal cord lesions", *Spinal Cord*, Vol. 37, No. 9 (1999) 634-37, Yokota T, Hirose K, Tanabe H, Tsukagoshi H, "Sleep related periodic leg movements (noctural myoclonus) due to spinal card lesion", *J. Neurol. Sci.*, Vol. 104, No. 1 (1991) 13-8.

4 Such as domperidone.

5 Wetter et al., "A randomized controlled study of pergolide in patients with restless legs syndrome", *Neurology*, Vol. 52, No. 5 (1999) 944-50.

does not at all increase the risk for Parkinson's disease.[6] For example, the prevalence of RLS in Parkinson's disease patients is approximately 10-15%, which is not significantly different than the prevalence of RLS in the general population, and which is also not significantly different than the prevalence of RLS in other conditions[7], i.e. 11.9 to 19.4% of pregnant women suffer from RLS, and 6 to 83% patients with end-stage renal disease suffer from RLS.[8] Kanda Declaration at ¶10.

For these reasons at least, Applicants respectfully submit it makes no more sense to treat RLS with Parkinson's disease medications than it would to treat RLS using drugs for renal disease or pregnancy. To the contrary, these results all indicate that RLS and Parkinson's disease do not share the same pathophysiologic mechanism.[9] Kanda Declaration at ¶11.

However, both disorders have dopaminergic dysfunction in the central nervous system - - A9 dopaminergic neurons are involved in Parkinson's disease, and A11 dopaminergic neurons may be involved in RLS. Certainly, as discussed above, central acting dopaminergic antiParkinsonian agents are effective in treating RLS since they correct the central nervous system. That is, such agents all have dopaminergic action in the CNS, i.e., L-DOPA is a dopamine precursor; pramipexol, ropinirole and rotigotine are

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[6] To the contrary, the common connection between RLS and Parkinson's disease appears to be only the iron deficiencies that can play a role in both conditions.

[7] Tan et al., "Restless legs syndrome in Parkinson's disease", *J. Neurol. Sci.*, Vol. 196 (2002) 33-6.

[8] Goodman et al., "Restless leg syndrome in pregnancy", *Brit. Med. J.*, Vol. 297, No. 6656 (1988) 1101-2; Collado-Seidel et al., "Clinical and biochemical findings in uremic patients with and without restless legs syndrome", *Am. J. Kidney Dis.*, Vol. 31, No. 2 (1998) 324-8.

[9] To the contrary, antiParkinsonian agents such as anticholinergics are not effective in treating RLS.

dopamine receptor agonists; and amantadine increases dopamine synthesis and release, or inhibits dopamine reuptake. Kanda Declaration at ¶12.

Thus, these agents treat RLS as only central acting dopaminergic agents, and not as antiParkinsonian agents.

That is to say, the person of ordinary skill in this art -- who understands RLS physiopathology -- also understands that there is no reason to arbitrarily administer antiParkinson disease medication to RLS patients unless such medication is also a central acting dopinamergic agent. In contrast to this, however, the compounds of the pending claims are not central acting dopinamergic agents. Rather, they are adenosine A2A receptor antagonists. Kanda Declaration at ¶13.

It is Applicants' unexpected discovery that adenosine A2A receptor antagonists have efficacy in treating RLS.

As to noctural myoclonus, such is a disorder characterized by aching or burning sensations in the lower (and rarely, the upper) extremities that occur prior to sleep, or may awaken the patient from sleep. The patient irresistibly moves the affected limbs to bring temporary relief, thus disrupting sleep and so, resulting in daytime hypersomnolence.[10] RLS differs essentially from noctural myoclonus in that in noctural myoclonus (i) the individual reports no adverse sensory stimuli and (ii) it is primarily a sleep-associated movement disorder[11], neither of which is true for RLS. Kanda Declaration at ¶14.

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[10] Harrison's Principles of Internal Medicine, 15th ed., 159.

[11] Adams, et al., *Principles of Neurology*, 6th ed., 387; *Schmerz Rundsch Med. Prax.*, Vol. 86, No. 18 (1997) 732-36.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 1-5 and 8-12 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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